## REMARKS

Claims 1-23 are pending in this application. Claims 18-21 have been withdrawn. Claims 1, 17, 20 and 21, have been amended.

Claim 1 has been amended to recite "A computer-implemented method for predicting at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of a predetermined reference protein or peptide, the at least one amino acid sequence having a biological activity essentially the same as a biological activity of the reference protein or peptide; which method comprises the steps of: a) providing a coordinate set representing the backbone of said 3D structure; b) constructing a reduced virtual representation for the 3D structure provide in step (a), wherein in said reduced representation, each amino acid has a backbone portion and a side chain portion, the backbone portion of each amino acid being represented by a single sphere and the side chain of each amino acid being represented by one to three additional spheres...." Specifically, step b of claim 1 now more clearly defines the reduced virtual representation for the 3D structure provided in step (a). Support for amended claim 1 can be found, for example, at page 8, line 27 to page 9, line 22 and throughout the specification and claims as originally filed. With regard to the backbone, page 9, lines 3-4, of the present specification describes that "the main chain of the protein, polypeptide or any other suitable polymer is represented by one virtual atom per residue." Regarding the side chain, page 9, lines 8 to 22, describes that the side chain of some amino acids are represented by one sphere, others by two spheres and the rest by three spheres.

Claims 17, 20 and 21 have been amended to correct minor typographical errors.

No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

***I. A page 2 of the Official Action, claim 17 is objected to.***

The Examiner notes that there appears to be a typographical errors in claim 17. Specifically, the Examiner asserts that it appears that the phrase "Claim 17, line 1, delete 'or claim 16" is recited in error. Further, the Examiner notes that it appears that the Applicants only want claim 17 to depend from claim 15. The Applicants thank the Examiner for these observations.

Applicants respectfully submit that in view of the amendment to claim 17 this objection has been obviated. Specifically, amended claim 17 now recites "The method as claimed in claim 15, wherein said de novo amino acid sequence stabilized said 3D structure, as compared to the native amino acid sequence." Accordingly, the Examiner is respectfully requested to withdraw this objection.

***II. At page 4 of the Official Action, claims 1-17, 22, and 23 are rejected under 35 USC § 101 for lack of utility.***

The Examiner asserts that the claimed subject matter is not supported by either a specific and substantial asserted utility or a well established utility. Specifically, the Examiner asserts that:

> the utility of predicting an amino acid sequence for a protein or peptide as instantly claimed lacks specificity or substantiality as to utility without some nexus to protein or peptide activity or binding reactions which will result in specific or substantial utility.

Applicants respectfully traverse this rejection.

Independent claim 1 is directed to "A ***computer-implemented*** method for predicting at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of a predetermined reference protein or peptide, the at least one amino acid sequence having a biological activity essentially the same as a biological activity of the reference protein or peptide ...." (Emphasis Added). The computer implemented method comprises a number of steps implemented on a computer which ultimately result in a virtually represented amino acid sequence which is expanded into its corresponding all-atom sequence representation thereby obtaining an amino acid sequence compatible with the predefined 3D, structure. Further, an optional computer output of the expanded all-atom representation may be obtained. Claims 2-17 and 22-23 depend, either directly or indirectly from claim 1.

The presently claimed subject matter provides a ***computer-implemented*** research method that has utility in the field of protein design. Applicants submit that the mere fact that sequences generated by the invention may require additional study in order to determine which sequences generated are useful, does not negate the utility of the presently claimed ***computer-implemented*** research tool. Therefore, Applicants submit that the presently claimed subject matter has specific, substantial and credible utility.

Applicants respectfully note that it appears that the Examiner is not properly evaluating the utility of the presently claimed subject matter as a ***computer-implemented*** method. Instead, it appears that the Examiner is solely interpreting the claims as a method of "predicting an amino acid sequence for a protein or peptide" without regard to the fact that the presently claimed subject matter is a computer-implemented method.

In this regard, Applicants direct the Examiner granted US Patent No 5,600,571, which recites:

> The present invention provides simulations of myoglobin carried out on a 16-node partition of a massively parallel CM-5 supercomputer. The vastly increased computing power of the CM-5 (equivalent to roughly 16 IBM 550 workstations) has been essential in designing a successful methodology. However, this would have been insufficient by itself; major modifications of the potential function and computational algorithm have also been required. On the order of $10^{10}$ structure evaluations are required to produce reasonable low resolution myoglobin structures and that complex simulated annealing strategies are needed to insure the efficient traversing of potential barriers. It is within the scope of the present invention that the same algorithm can be used to fold a wide variety of proteins to the same resolution, including those containing β-sheets. *See* US 5,600,571 at column 3, lines 1-15.

Like the presently claimed subject matter, US 5,600,571 is directed to computer methods to determine protein structure. In this regard, claim 1 of US 5,600,571 is merely directed to:

> A method for determining the most stable tertiary structure of a protein having a known primary structure which comprises the steps of (a) producing a reduced representation of the protein by assigning to the protein (i) secondary structural motifs comprising loops and helices present therein and (ii) all φ and Φ dihedral angles for the amino acid residues present therein; (b) determining which conformations of the reduced representation are physically permissible (c) determining which of the physically permissible conformations of the protein possesses the lowest free energy which comprises the steps of (i) randomly varying the dihedral angles of each

> conformation and evaluating energy for each conformation using a dipole approximation, (ii) accepting or rejecting a conformation in accordance with Metropolis test criteria, (iii) iterating steps (c)(i) and (ii) on accepted conformations and generating $C_\alpha$ and if present $C_\beta$ atomic coordinates for all residues, and (iv) evaluating energy using the atomic coordinates and a full potential function for all conformations to provide an ensemble of low energy conformations; and (d) comparing conformations to determine that of lowest energy, so as to thereby determine the most stable tertiary structure of the protein. *See* US 5,600,571.

Evaluated by a person of ordinary skill in the art of **computer-implemented methods**, the presently claimed subject matter would clearly have utility. Regarding specific utility, the presently claimed subject matter provides "A ***computer-implemented*** method for predicting at least one amino acid sequence that folds into a specified three-dimensional (3D) structure of a predetermined reference protein or peptide, the at least one amino acid sequence having a biological activity essentially the same as a biological activity of the reference protein or peptide ...." (Emphasis added). As required, the presently claimed computer-implemented method is *specific* to the subject matter claimed and can provide a well-defined and particular benefit to the public." *See* MPEP § 2107.01.

Further, the presently claimed subject matter has substantial utility. According to MPEP § 2107.01, "Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *In re Fisher*, 421 F.3d at 1371, 76 USPQ2d at 1230. The presently claimed subject matter's significant and presently available benefit to the public is that it is a **computer-implemented method**.

The Examiner indicates that:

> It is noted that no well established utility has been asserted or is known for generic amino acid sequence prediction without some utility for the resultant protein or peptide. *See* Official Action at page 5.

However, Applicants submit that the presently claimed subject matter is directed to a **computer-implemented** method; therefore, ***the utility rests in the computer mediated method, and not in the amino acid sequences predicted***.

In view of the foregoing, Applicants submit that the presently claimed subject matter has utility within the meaning of 35 USC § 101. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

***III. At page 7 of the Official Action, claims 1-17, 22 and 23 are rejected under 35 USC § 112, first paragraph.***

The Examiner asserts that "since the claimed invention is not supported by a substantial, specific utility or well established utility, one of skill in the art clearly would not know how to use the claimed invention."

Applicants traverse this rejection.

As discussed above, the presently claimed subject matter clearly has utility as a **computer-implemented** method. A person of ordinary skill in the art, i.e., **a computer scientist with biotechnology experience**, would know how to practice the claimed invention. As evidence of this, Applicants respectfully refer the Examiner to the entirety of granted US Patent No. 5,600,571 (reproduced in part above), which is directed to similar subject matter to that of the presently pending claims. Again applicants maintain the

position that the utility of the present invention does not simply lie in the amino acid sequences; but the utility lies in, and consequently should be evaluated as, the computer mediated process presently claimed.

In view of the foregoing, Applicants submit that the presently claimed subject matter has utility within the meaning of 35 USC § 112, first paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

***IV. At page 8 of the Official Action, claims 1-17, 22 and 23 are rejected under 35 USC § 103 as being unpatentable over Dahiyat et al., and further in view of Hurley et al.***

Regarding claims 1-5, 9-17 and 22, the Examiner asserts that it would have been obvious to one of ordinary skill in the art to incorporate the representation taught by Hurley et al. (JMB Vol. 224, 1992, pp. 1143 to 1159) with the method of Dahiyat et al. (Protien Science, 1996, Vol. 5, pp. 895-903) to gain the benefit of being able to determine the structural changes of a protein or peptide. Regarding claims 6-8, the Examiner asserts that it would have been obvious to combine the teaching of Dahiyat et al. with those of Hurley et al to determine the structure of an amino acid in water because it would have allowed for the calculation of stability change.

Applicants respectfully traverse this rejection because *prima facie* case of obviousness has not been established.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) some suggestion or motivation to modify the references exists; (2) a reasonable expectation of success; and (3) the prior art references teach or suggest all of the claim

limitations. *Amgen, Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); *In re Fine,* 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970).

It is submitted that a *prima facie* obviousness has not been established because, whether considered alone or in combination, none of Dahiyat et al. or Hurley et al. teach or suggest all of the limitations of the presently pending claims.

As discussed, independent claim 1 is directed to 1 "A computer-implemented method for predicting least one amino acid sequence that folds into a specified three-dimensional (3D) structure of a predetermined reference protein or peptide, the at least one amino acid sequence having a biological activity essentially the same as a biological activity of the reference protein or peptide; which method comprises the steps of: a) providing a coordinate set representing the backbone of said 3D structure; b) constructing a reduced virtual representation for the 3D structure provide in step (a), wherein in said reduced representation, each amino acid has a backbone portion and a side chain portion, the backbone portion of each amino acid being represented by a single sphere and the side chain of each amino acid being represented by one to three additional spheres; c) determining for each amino acid position along the virtual structure representation provided in step (b) its solvent accessibility; d) constructing an initial amino acid sequence by assigning for each amino acid position along the structure an amino acid residue selected randomly from a predefined group of amino acids having a solvent accessibility compatible with the solvent accessibility of said position; e) randomly selecting one or more positions along the sequence provided in step (d) and applying on each

position a Monte-Carlo simulation in sequence space and rotamer space, said simulation comprising one or more scoring function calculating steps which include: i) randomly selecting one or more amino acid residues of the same solvent accessibility as that defined for said position to obtain a mutation; ii) calculating an energy difference delta E, between the predetermined protein or peptide and each mutated amino acid residue provided in step (i) based on its said reduced virtual representation; iii) selecting a rotamer having a minimal delta E, or when more than one amino acid are manipulated simultaneously, selecting a rotamer combination having a minimal delta E; iv) accepting the mutation with the rotamer or rotamer combination selected in step (iii) if delta E<0; and v) assigning the amino acid residue or residues and their respective selected rotamer or rotamer combinations selected in step (iii) to said position/s and moving to another position along the sequence; wherein said simulation steps are repeated until for each position along said sequence, the residue and residue's rotamer with the lowest energy score is selected, to obtain a virtually represented amino acid sequence with the lowest total energy score; f) expanding the reduced representation of the virtually represented amino acid sequence obtained in step (e) to its corresponding all-atom sequence representation thereby obtaining an amino acid sequence compatible with the predefined 3D structure; and g) optionally, creating a computer output of the expanded all-atom representation of the primary structure/s obtained in step (f)." Claims 2-27 and 22-23 depend, either directly or indirectly from claim 1.

As discussed at page 10 of the Office Action, Dahiyat et al. does not teach or suggest representing an amino acid by two or more spheres. In contrast, Hurley et al.

teaches that every atom is represented by an individual atom. *See* Figs. 1 to 3 Hurley et al.

Neither Dahiyat et al. nor Hurley et al. teach or suggest representing an amino acid by two to four spheres. As discussed step b of claim 1 recites "constructing a reduced virtual representation for the 3D structure provide in step (a), wherein in said reduced representation, each amino acid has a backbone portion and a side chain portion, the backbone portion of ***each amino acid being represented by a single sphere and the side chain of each amino acid being represented by one to three additional spheres....***" (Emphasis added). Accordingly, the presently claimed subject matter teaches *inter alia* representing an amino acid by two to four spheres.

Applicants note that representing the backbone of an amino acid in the sequence by one sphere and the side chain by one to three spheres takes into account rotation about the three major dihedral angles of the amino acid. As recognized by those skilled in the art, this is not possible when each amino acid is represented by only one sphere (as taught by Dahiyat et al.) while reducing computational complexity in comparison to each atom in the amino acid being represented by a single sphere (as taught by Hurley et al.). Therefore, Applicants submit that whether taken alone, or in combination, none of Dahiyat et al. and Hurley et al. teach or suggest each limitation of the presently claimed subject matter.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, Dahiyat et al. and Hurley et al. do not render the presently pending claims obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

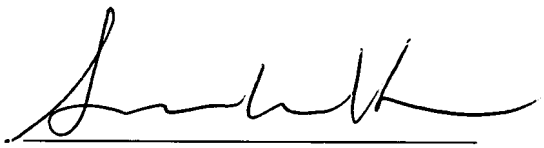
**Conclusion**

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

**THE NATH LAW GROUP**



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